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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT
OF HEPATOCELLULAR CARCINOMA
BACKGROUND OF THE INVENTION

Thalidomide was first synthesized in 1953, and it was widely used as a sedative and for the prevention of vomiting during pregnancy. In 1963, it was found that women who took thalidomide in the first trimester of pregnancy would deliver terata, such as phocomelia. Therefore, thalidomide was prohibited in Europe and the USA.

In view of studies in recent years thalidomide has been found to affect the immune system which may treat immune system related diseases. For instance, Arch Dermatol. 1993, vol. 129, p. 1548-1550 describes the use of thalidomide in the treatment of cutaneous lupus erythematosus; the Journal of Rheumatology, 1989, 16, p. 159-163 describes the use of thalidomide in the treatment of refractory rheumatoid arthritis; Arch Dermatol. 1990, vol. 126, p. 923-927 describes the use of thalidomide in the treatment of Behcet's syndrome; Journal of Pediatr. Gastroenterol. Nurt. 1999, vol. 28, p. 214-216 describes the use of thalidomide in the treatment of Cornh's disease; and Journal of Rheumatology, 1998, vol. 25, p. 964-969 describes the use of thalidomide in the treatment of rheumatoid arthritis. In addition, U.S. Patent Nos. 5,593,990 and 5,629,327 disclose that thalidomide could effectively inhibit angiogenesis; U.S. Patent No. 5,654,312 discloses the methods of treatment for inflammatory and autoimmune dermatoses. In addition, the Journal of Infectious Diseases, 1993, 168, p. 408-414 teaches that thalidomide could effectively inhibit tumor necrotic factor-alpha (TNF-I). Anti-Cancer Drugs, 1996, 7, p. 339-343 demonstrates that thalidomide could effectively inhibit basic fibroblast growth factor-induced angiogenesis. Thalidomide is widely used in the clinical treatment of malignant tumors which are highly vascular and cannot be effectively treated by chemical therapy. For instance, U.S. Patent No. 5,696,092 discloses the use of thalidomide in the inhibition of metastases of cancers of epithelial cell origin, especially human prostate cancers. Among the above prior art references, none of the references or patents teach that thalidomide could be specifically used in the treatment of hepatocellular carcinoma.

Up to the present time, there are no drugs that can effectively treat hepatocellular carcinoma. Patients suffering from metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, normally survive for three to four months. Metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, is treated by systemic therapy. The use of Doxorubicin, or a high dosage of Tamoxifen in combination with

Doxorubicin or EA-PFL (etoposide, adrimycin, cisplatin, fluorouracil and leucovorin), is an effective example. The remission rate of those drugs can achieve levels between 15 and 30%. However, because the patients suffering from hepatocellular carcinoma usually develop complications such as liver cirrhosis, leukopenia, thrombopenia or liver function impairment, they cannot be subject to systemic chemotherapy.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a pharmaceutical composition for use in the treatment of hepatocellular carcinoma.

Another object of the present invention is to provide a pharmaceutical composition for use in the treatment of metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, which comprises thalidomide and a pharmaceutically acceptable carrier.

Another object of the present invention is to provide a pharmaceutical composition for use as adjuvant treatment for patients of hepatocellular carcinoma, where local treatment has failed. The local treatment may be percutaneous ethanol injection, operation, transcatheter arterial chemoembolization (TACE) or cryotherapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1-4 show computerized abdominal tomography of a patient, before and after treatment with thalidomide.

Figures 1 and 2: show before the treatment with thalidomide and the computerized abdominal tomography scan shows that the left and right hepatic lobes of the patient were infiltrated with diffused hepatocellular carcinoma. The depositing of Lipiodol on the liver lobes after arterial embolization is shown in Figures 1 and 2.

Figure 2 also shows a 5 cm x 5 cm massive type index lesion at the left hepatic lobes. The serum level of alpha-fetoprotein in the patient is 4335 μ g/ml.

Figures 3 and 4: show after the treatment with thalidomide. The computerized abdominal tomography scan shows that most of the diffused hepatocellular carcinoma, which infiltrated the left and right hepatic lobes of the patient, disappeared. The massive type index lesion at the left hepatic lobe shown in Figure 3 has been reduced to the size of 3 cm x 3 cm. The serum level of alpha-fetoprotein in the patient is 1501 μ g/ml. In addition, the scan shows the occurrence of ascitic fluid. After the detection by abdominal paracentesis, it is proved that the occurrence of ascitic fluid was caused by spontaneous bacterial peritonitis, and hepatocellular carcinoma does not exist.

Figures 5-7 show the variation of the serum level of alpha-fetoprotein in three individual patient before and after the treatment with thalidomide.

Example 1 of the present invention describes capsules comprising

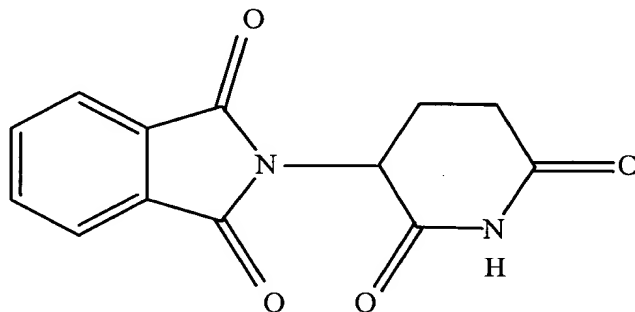
thalidomide.

Examples 2 and 3 of the present invention describe patients being treated with thalidomide.

DETAILED DESCRIPTION OF THE INVENTION

5 The present invention uses thalidomide to treat metastatic hepatocellular carcinoma and hepatocellular carcinoma, where local treatment has failed. The inventors found that thalidomide has excellent effects concerning the treatment of such carcinomas which are difficult to treat. This includes the significant and rapid decrease of the serum level of alpha-fetoprotein, the reduction of the size of
10 tumors and the relief of symptoms for patients, without significant side effects, such as arrest of bone marrow or hepatotoxicity.

 The chemical nomenclature of thalidomide used in the subject invention is 2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione, which is a white crystal powder; odorless; mp 269-271°C; sparingly soluble in water, methanol, ethanol or
15 acetone. The chemical structure of thalidomide is as follows:



20 The term "pharmaceutically effective amount" used in the pharmaceutical composition of the present invention is directed to the amount to mammals that need such treatment in order to proceed with the above-mentioned treatment. The pharmaceutically effective amount depends on the individual, the disease to be treated, the body weight and age of the individual, the level of the disease or the administration route. This can be determined by persons skilled in the art. The
25 pharmaceutically effective amount of thalidomide used in the subject invention is 30 to 1200 mg for an adult for a daily dose of oral administration, preferably 50 to 800 mg and more preferably 100 to 500 mg.

 The pharmaceutical composition of the present invention can be used in combination with other hepatocellular carcinoma treating drugs, such as
30 anticancer chemotherapeutic drugs, hormones, biological response modifier(s), other angiogenesis inhibitors; or in combination with immunotherapy or gene therapy.

 The pharmaceutical composition of the present invention can be

administered by different routes, comprising oral, rectal, topical, subcutaneous, intravenous, intramuscular and nasal administration. The compound is effective in both injection or oral formulation.

5 The pharmaceutical composition of the present invention can be formulated by use of conventional techniques and can be formulated into such discrete dosage forms, including capsules, cachets, tablets, granules or pills; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus; together with suitable a pharmaceutically acceptable carrier. For instance, a tablet may be made by
10 compression or molding, optionally with one or more excipient or carrier ingredients. Compressed tables may be prepared by compressing, in a suitable machine, thalidomide in a free-flowing form such as a powder or granules, mixed with a binder, flavoring agent, solubilizer, lubricant, inert diluent, preservative, surface active or dispersing agent. The tablet may be optionally coated or formulated so as to provide a
15 controlled release of thalidomide.

The therapeutic efficacy of the pharmaceutical composition of the present invention comprising thalidomide for the treatment of hepatocellular carcinoma has been supported by clinical observation as illustrated in the following examples.

20

Example

Example 1

Capsules each containing 50 mg of thalidomide were made as follows: thalidomide 50 mg, lactose 50 mg, corn starch 18 mg, and Avicel 65 mg, were blended, passed through a No. 45 mesh sieve, and filled into hard gelatin capsules.

25

Example 2

A 44 year-old male patient weighing 55 kg with a medical history of hepatitis C was diagnosed with hepatocellular carcinoma in December 1998 and treated with transcatheter arterial chemoembolization. He was treated with transcatheter arterial chemoembolization again in March and June 1999. According to
30 the computerized abdominal tomography and gastrointestinal track barium enema, hepatocellular carcinoma invasion of the right colon and duodenum was detected. The patient was treated with radiation on the right liver lobe during July to September 1999. After one-month of treatment, the serum level of alpha-fetoprotein in the patient increased from 105 μ g/ml, before treatment, to 535 μ g/ml. The follow-up magnetic
35 resonance imaging (MRI) revealed that the hepatocellular carcinoma of the patient was exacerbated and complicated with tumor thrombosis of a portal vein. The patient was further treated with a transcatheter arterial chemoembolization. The serum level of

alpha-fetoprotein in the patient was increased to 1572 μ g/ml.

In November 1999, the follow-up computerized abdominal tomography scan showed that the two hepatic lobes of the patient had wide hepatocellular carcinoma infiltration (as shown in Figs. 1(a) and 1(b)), esophageal and gastric varices, tumor thrombosis of a portal vein and the main portal vein in the liver. The serum level of alpha-fetoprotein in the patient was up to 4335 μ g/ml. The liver function exacerbated that the total bilirubin was 9.2 mg/ml, GOT/GPT was 253/115 IU and alkaline phosphase (ALP) was 239 unit/l. Because the liver function of the patient was so bad, he was not suited to take transcatheter arterial embolization therapy. A capsule containing 100 mg of thalidomide was orally administered to the patient twice daily during the thalidomide treatment. After two weeks of treatment, right upper quadrant tenderness of the patient was significantly relieved. After four weeks, the serum level of alpha-fetoprotein in the patient was decreased to 1501 μ g/ml, total bilirubin was 10.2 mg/ml, GOT/GPT was 184/102 IU and alkaline phosphase was 233 unit/l. Meanwhile, the follow-up MRI showed that the hepatocellular carcinoma of the two liver lobes significantly remission (as shown Figures 3 and 4). However, ascitic fluid was found. The abdominal paracentesis evidenced that ascitic fluid was caused by spontaneous bacterial peritonitis. The hepatocellular carcinoma did not exist. The patient was then administered with antibiotics for the treatment of spontaneous bacterial peritonitis. The patient was still treated with thalidomide to the present. Figure 5 shows the variation of the serum level of alpha-fetoprotein in the patient. After treatment with thalidomide, the serum level of alpha-fetoprotein significantly decreased.

Example 3

Two patients with metastatic and locally advanced hepatocellular carcinoma who were unable to have or local treatments failed were subjected to thalidomide treatment. Thalidomide was administered 100 mg twice daily. They were subjected to a serum alpha-fetoprotein test every 2-4 weeks and computed tomography or magnetic resonance image examination every 4-8 weeks. As shown in Figures 6 and 7, serum alpha-fetoprotein level in the two patients was significant reduced after thalidomide treatment.

ABSTRACT OF THE INVENTION

The invention discloses a pharmaceutical composition for use in the treatment of hepatocellular carcinoma, which comprises thalidomide and a pharmaceutically acceptable carrier.

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[described] describes the use of thalidomide in the treatment of cutaneous lupus
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thalidomide in the treatment of Behcet's syndrome; Journal of Pediatr. Gastroenterol.
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[described] describes the use of thalidomide in the treatment of rheumatoid arthritis.
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effectively inhibit angiogenesis; U.S. Patent No. 5,654,312 discloses the methods of
treatment for inflammatory and autoimmune dermatoses. In addition, the Journal of
Infectious Diseases, 1993, 168, p. 408-414 [taught] teaches that thalidomide could
effectively inhibit tumor necrotic factor-alpha (TNF-I). Anti-Cancer Drugs, 1996, 7, p.
25 339-343 [demonstrated] demonstrates that thalidomide could effectively inhibit basic
fibroblast growth factor-induced angiogenesis. Thalidomide is widely [applied] used
in the clinical treatment of malignant tumors which are highly vascular and cannot be
effectively treated by chemical therapy. For instance, U.S. Patent No. 5,696,092
discloses the use of thalidomide in the inhibition of metastases of cancers of epithelial
30 cell origin, especially human prostate cancers. Among the above prior art references,
none of the references or patents [teaches] teach that thalidomide could be specifically
used in the treatment of hepatocellular carcinoma.

 Up to the present time, there are [not any] no drugs that can effectively
treat hepatocellular carcinoma. Patients [with] suffering from metastatic
35 hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has
failed, normally survive for [only] three to four months. Metastatic hepatocellular
carcinoma or hepatocellular carcinoma, where local treatment has failed, is [mainly

subjected to] treated by systemic therapy. The use of Doxorubicin, or a high dosage of Tamoxifen in combination with Doxorubicin or EA-PFL (etopoxide, adrimycin, cisplatin, fluorouracil and leucovorin), is an effective example. The remission rate of those drugs can achieve levels between 15 and 30%. However, because the patients
5 [of] suffering from hepatocellular carcinoma usually develop [complication of] complications such as liver cirrhosis, [and other complications (such as] leukopenia, thrombopenia or liver function impairment, they cannot be subject to systemic chemotherapy.

SUMMARY OF THE INVENTION

10 An object of the present invention is to provide a pharmaceutical composition for use in the treatment of hepatocellular carcinoma.

Another object of the present invention is to provide a pharmaceutical composition for use in the treatment of metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, which comprises
15 thalidomide and a pharmaceutically acceptable carrier.

Another object of the present invention is to provide a pharmaceutical composition for use as adjuvant treatment for patients of hepatocellular carcinoma, where local treatment has failed. The local treatment may be percutaneous ethanol injection, operation, transcatheter arterial chemoembolization (TACE) or cryotherapy.

BRIEF DESCRIPTION OF THE DRAWINGS

20 Figures 1-4 show computerized abdominal tomography of a patient, before and after treatment with thalidomide.

Figures 1 and 2: show before the treatment with thalidomide and the computerized abdominal tomography scan shows that the left and right hepatic lobes
25 of the patient were infiltrated with diffused hepatocellular carcinoma. The depositing of Lipiodol on the liver lobes after arterial embolization is shown in Figures 1 and 2.

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Figures 3 and 4: show after the treatment with thalidomide. The
30 computerized abdominal tomography scan shows that most of the diffused hepatocellular carcinoma, which infiltrated the left and right hepatic lobes of the patient, disappeared. The massive type index lesion at the left hepatic lobe shown in Figure 3 has been reduced to the size of 3 cm x 3 cm. The serum level of alpha-fetoprotein in the patient is 1501 μ g/ml. In addition, the scan shows the
35 occurrence of ascitic fluid. After the detection by abdominal paracentesis, it is proved that the occurrence of ascitic fluid was caused by spontaneous bacterial peritonitis, and hepatocellular carcinoma does not exist.

Figures 5-7 show the variation of the serum level of alpha-fetoprotein in three individual patient before and after the treatment with thalidomide.

Example 1 of the present invention describes capsules comprising thalidomide.

5 Examples 2 and 3 of the present invention describe patients being treated with thalidomide.

[SUMMARY OF THE INVENTION]

An object of the subject invention is to provide a pharmaceutical composition for use in the treatment of hepatocellular carcinoma.

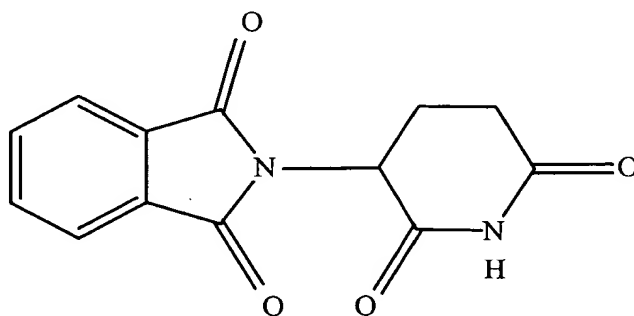
10 Another object of the subject invention is to provide a pharmaceutical composition for the use in the treatment of metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, which comprises thalidomide and a pharmaceutically acceptable carrier.

15 Another object of the subject invention is to provide a pharmaceutical composition used as adjuvant treatment for patients of hepatocellular carcinoma who have failed to local treatment, such as percutaneous ethanol injection, operation, transcatheter arterial chemoembolization (TACE) or cryotherapy.]

DETAILED DESCRIPTION OF THE INVENTION

20 The present [subject] invention [utilizes] uses thalidomide to treat metastatic hepatocellular carcinoma and hepatocellular carcinoma, where local treatment has failed. The [invention] inventors found that thalidomide has excellent effects concerning the treatment of such carcinomas which are difficult to treat. This includes the significant and rapid decrease of the serum level of alpha-fetoprotein, the reduction of the size of tumors and the relief of symptoms for patients, without
25 significant side effects, such as arrest of bone marrow or hepatotoxicity.

 The chemical nomenclature of thalidomide used in the subject invention is 2-(2,6-dioxo-3-piperidiny)-1H-isoindole-1,3(2H)-dione, which is a white crystal powder; odorless; mp 269-271°C; sparingly soluble in water, methanol, ethanol or acetone. The chemical structure of thalidomide is as follows:



The term "pharmaceutically effective amount" used in the pharmaceutical composition of the [subject] present invention is directed to the [administered] amount to mammals that need such treatment in order to proceed with the above-mentioned treatment. The pharmaceutically effective amount depends on the individual, the disease to be treated, the body weight and age of the individual, the level of the disease or the administration route. This can be determined by persons skilled in the art. The pharmaceutically effective amount of thalidomide used in the subject invention is 30 to 1200 mg for an adult for a daily dose of oral administration, preferably 50 to 800 mg and more preferably 100 to 500 mg.

The pharmaceutical composition of the [subject] present invention can be used in combination with other hepatocellular carcinoma treating drugs, such as anticancer chemotherapeutic drugs, hormones, biological response modifier(s), other angiogenesis inhibitors; or in combination with immunotherapy or gene therapy.

The pharmaceutical composition of the [subject] present invention can be administered by different routes, comprising oral, rectal, topical, subcutaneous, intravenous, intramuscular and nasal administration. The compound is effective in both [injective formulation] injection or oral formulation.

The pharmaceutical composition of the [subject] present invention can be formulated by use of conventional techniques and can be formulated into such [as] discrete dosage forms, [such as] including capsules, cachets, tablets, granules or pills; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus; together with suitable a pharmaceutically acceptable carrier. For instance, a [table] tablet may be made by compression or molding, optionally with one or more excipient or carrier ingredients. Compressed tables may be prepared by compressing, in a suitable machine, thalidomide in a free-flowing form such as a powder or granules, mixed with a binder, flavoring agent, solubilizer, lubricant, inert diluent, preservative, surface active or dispersing agent. The [table] tablet may be optionally coated or formulated so as to provide a controlled release of thalidomide.

The therapeutic efficacy of the pharmaceutical composition of the [subject] present invention comprising thalidomide [on] for the treatment of hepatocellular carcinoma has been supported by clinical observation as illustrated in the following examples.

Example

Example 1

Capsules each containing 50 mg of thalidomide were made as follows: thalidomide 50 mg, lactose 50 mg, corn starch 18 mg, and Avicel 65 mg, were

blended, passed through a No. 45 mesh sieve, and filled into hard gelatin capsules.

Example 2

A 44 year-old male patient [weighted] weighing 55 kg with a medical history of hepatitis C was diagnosed with hepatocellular carcinoma in December 1998 and treated with transcatheter arterial chemoembolization. He was treated with transcatheter arterial chemoembolization again in March and June 1999. According to the computerized abdominal tomography and gastrointestinal track barium enema, hepatocellular carcinoma invasion of the right colon and duodenum was [doubted] detected. The patient was treated with radiation on the right liver lobe during July to September 1999. After one-month of treatment, the serum level of alpha-fetoprotein in the patient increased from 105 μ g/ml, before treatment, to 535 μ g/ml. The follow-up magnetic resonance imaging (MRI) revealed that the hepatocellular carcinoma of the patient was exacerbated and [was] complicated with tumor thrombosis of a portal vein. The patient was further treated with a [forth] transcatheter arterial chemoembolization. The serum level of alpha-fetoprotein in the patient was increased to 1572 μ g/ml.

In November 1999, the follow-up computerized abdominal tomography scan showed that the two hepatic lobes of the patient had wide hepatocellular carcinoma infiltration (as shown in Figs. 1(a) and 1(b)), esophageal and gastric varices, tumor thrombosis of a portal vein and the main portal vein in the liver. The serum level of alpha-fetoprotein in the patient was up to 4335 μ g/ml. The liver function exacerbated that the total bilirubin was 9.2 mg/ml, GOT/GPT was 253/115 IU and alkaline phosphase (ALP) was 239 unit/l. [As] Because the liver function of the patient was [significantly exacerbated] so bad, he was not [suitable] suited to take transcatheter arterial embolization therapy. A capsule containing 100 mg of thalidomide was orally administered to the patient twice daily during the thalidomide treatment. After two weeks of treatment, right upper quadrant tenderness of the patient was significantly relieved. After four weeks, the serum level of alpha-fetoprotein in the patient was decreased to 1501 μ g/ml, total bilirubin was 10.2 mg/ml, GOT/GPT was 184/102 IU and alkaline phosphase was 233 unit/l. Meanwhile, the follow-up MRI showed that the hepatocellular carcinoma of the two liver lobes significantly [remitted] remission (as shown Figures 3 and 4). However, ascitic fluid was found. The abdominal paracentesis evidenced that ascitic fluid was caused by spontaneous bacterial peritonitis. The hepatocellular carcinoma did not exist. The patient was then administered with antibiotics for the treatment of spontaneous bacterial peritonitis. The patient was still treated with thalidomide to the present. Figure 5 shows the variation of the serum level of alpha-fetoprotein in the patient. After treatment with thalidomide, the serum level of alpha-fetoprotein significantly decreased.

Example 3

Two patients with metastatic and locally advanced hepatocellular carcinoma who were unable to have or [had failed to] local treatments failed were subjected to thalidomide treatment. Thalidomide was administered 100 mg twice
5 daily. They were subjected to a serum alpha-fetoprotein test every 2-4 weeks and computed tomography or magnetic resonance image examination every 4-8 weeks. As shown in Figures 6 and 7, serum alpha-fetoprotein level in the two patients was significant reduced [by] after thalidomide treatment.

ABSTRACT OF THE INVENTION

The invention [mainly] discloses a pharmaceutical composition for use in the treatment of hepatocellular carcinoma, which comprises thalidomide and a pharmaceutically acceptable carrier.